



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/802,249

03/17/2004

Ralf Mauritz

WP21718US

5270

23690

7590

12/10/2008

ROCHE DIAGNOSTICS OPERATIONS INC.

9115 Hague Road

Indianapolis, IN 46250-0457

EXAMINER

LIU, SUE XU

ART UNIT

PAPER NUMBER

1639

MAIL DATE

DELIVERY MODE

12/10/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/802,249	Applicant(s) MAURITZ ET AL.	
	Examiner SUE LIU	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/27/08.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 12, 13 and 15-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 12, 13 and 15-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Status

1. Claims 4-11, 14 and 23-26 have been cancelled as filed on 2/12/08.
Claims 1-3, 12, 13, and 15-22 are currently pending.
Claims 1-3, 12, 13 and 15-22 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of Group I (Claims 1-22) in the reply filed on 10/18/06 is as previously acknowledged.
3. Applicant's election without traverse of the following species:
A.) nucleic acids for the biopolymers;
B.) fluorescent groups, specifically, stilbene, as the detectable protecting groups;
C.) Compound (f) in Figure 5 as the core structure;
in the reply filed on 10/18/06 and 3/6/07 is as previously acknowledged.

Priority

4. This application claims foreign priority to EPO 03006098.2 (3/19/03).
5. Receipt is as previously acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Art Unit: 1639

Claim Rejections Withdrawn

6. In light of applicants' amendments to the claims as well as applicant's arguments, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claims 1-3, 12, 13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B.) Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

McGall and Others

9. Claims 1-3, 12, 13 and 15-22 are rejected under **35 U.S.C. 103(a)** as being unpatentable over **McGall** et al (US 6,238,862; 05/29/2001), **Wagner** et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04), in view of **Hobbs** et al (5,151,507; 9/29/1992; cited previously) and if necessary, **Chen** et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and **Agris** (PGPUB 20020045167; 4/18/2002; cited previously). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

The instant claims recite a “quality control method for determining degree of deprotection of protected reactive groups in manufacturing a biopolymer array, the method comprising

(a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups coupled directly to the building blocks, wherein at least some of the detectable protecting groups couple directly to amino groups of the building blocks and remain coupled until synthesis is terminated,

(b) after synthesis is terminated, achieving a degree of deprotection by taking one or more steps to cleave the detectable protecting groups,

(c) carrying out a determination of a degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage, and

(d) repeating steps (b) and (c) if detectable protecting groups are detected, wherein the quality control method is performed on the array.”

McGall et al, throughout the patent, teach methods of quality control for manufacturing nucleic acid probe arrays (e.g. Abstract and Claim 1 of the reference), which reads on the quality control method of **clm 1**.

The reference teaches synthesizing nucleic acids using protected monomers (e.g. Claims 5, 12 and 23; col. 2, lines 40+; Figures 9-10; col.4, lines 51+), which reads on step (a) of **clm 1** and nucleic acids of **clm 12**. The protected monomers read on the “detectable protecting groups coupled directly to the building blocks” as recited in **clm 1**.

The reference teaches “deprotecting” (or removal) of the protecting group at the end of each round of synthesis (e.g. Claim 23; col. 2, lines 40+; Figure 9), which reads on step (b) of **clm 1**. The instant claim language (step b) of claim 1) can be broadly interpreted to mean after the termination of any synthesis step, for example, after each round of synthesis (i.e. after the end of each cycle). The reference teaches, for example, “photolabile groups” (i.e. protection groups) and “side chain protective groups” are removed after the desired products are produced (e.g. col.5, lines 2), which reads on the step of cleaving the protecting groups as recited in step (b) of **clm 1**.

The reference teaches “determining the amount of unprotected active sites” (col. 2, lines 49+) by detecting the amount “detectable labels” on the array (col. 2, lines 40+; cols. 8-9; Figure 7; especially, col.9, lines 9+), which reads on step (c) of **clm 1**.

The reference also teaches repeating steps of “deprotection” (e.g. claim 12), which reads on the optionally repeated deprotection step of **clm 1**.

Art Unit: 1639

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a rhodamine (e.g. Claims 26 and 27 of the reference), which reads on the “fluorescent groups” of **clm 2** and rhodamine of **clm 3**.

The reference teaches the fluorescent label is linked (or coupled) to the nucleotide (e.g. Figure 6), which reads on the “coupled to nucleobases” of **clm 13**. The instant specification and/or claims do not specifically define the phrase “coupled to nucleobase”. The phrase can be broadly interpreted to mean coupling the “protection group” (e.g. fluorescent label) and the “nucleobase” through any type of linkage (including both direct and indirect linkage). The reference teaches linking the fluorescent label through the phosphate group in the sugar group of the nucleotide (e.g. Figure 6), and thus the label is “coupled” to the nucleobase of the nucleotide.

McGall et al do not explicitly teach the protection groups are directly coupled to and protect the nucleobase amino groups as recited in the amended **clm 1**. The reference also does not explicitly teach the optional repeating steps of deprotection and detection as recited in the amended **clm 1**. The reference also does not teach using “stilbene” (the elected species) as the “fluorescent group”, as recited in **clm 3**. The reference also does not explicitly teach the various chemistries recited in **clms 15-22**.

However, McGall et al., teach repeating steps of “deprotection” (e.g. claim 12). It would have been prima facie obvious for one of ordinary skill in the art to optionally repeat both the deprotection and detection steps for the desired results measuring deprotection at different stages. It would have been obvious to one of ordinary skill in the art to apply the standard technique of repeating deprotection and detection steps as the procedure for performing the said steps are taught by McGall, to improve the deprotection (such as to render various degrees of

Art Unit: 1639

deprotection) and detection (such as to generate an average measurements) for the predictable result of enabling standard oligonucleotide synthesis and the accompanying quality control measurements.

Wagner et al, throughout the publication, teach methods of nucleic acid synthesis using protected nucleotides. (see Abstract). The reference teaches synthesis of various oligonucleotides using protected nucleotides (pp. 204-206; especially Table 1 and p. 204, last para). The reference teaches the fluorescent label is linked directly to the amino group of the nucleobases (e.g. p. 202, Schemes 1-2), which reads on the “coupled to nucleobases” of **clm 13**, and coupling through the amino groups of **clm 1**. The reference also teaches detecting the protecting groups attached to the synthesized oligonucleotides (e.g. pp.206-207). The reference also teaches deprotecting the label attached nucleobase after the synthesis of the oligonucleotide (e.g. pp.205-206; Figure on pg.206), which reads on the “at least some of the detectable protecting groups couple directly to amino groups of the building blocks and remained coupled until synthesis terminated” as recited in **clm 1**.

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a “dnseoc” (or a “dansyl”) (e.g. p. 201, para 3 and Figures), which reads on the “fluorescent groups” of **clm 2** and “dansyl” of **clm 3**. The “dnseoc” ((dansylethoxy)carbonyl) group also reads on the “L” group when n=1 (as recited in **clm 21**), because the carbonyl group reads on the formula “C(O)” and the dansyl group reads on formula “R”.

The reference also teaches the structure of nucleotides comprising a base (protected by dnseoc), a sugar, a protected hydroxyl group, and a protected phosphate group (e.g. Scheme 2, Scheme 5). The (MeO)₂TrO (or Dimethoxytrityl) group in Scheme 5 of the reference (see p. 201,

Art Unit: 1639

para 4 and p. 204) reads on the hydroxyl protection group, DMTrO (the elected species of ; see Reply, filed 3/6/07, p. 2) or the “triphenylmethyl” group of **clms 15, 16, and 17**.

The reference also teaches phosphate protection group such as the “(2-cyanoethoxy)bis(diisopropylamino)phosphine” at the 3’ sugar position (p. 204, para 1 and Scheme 5), which is the same phosphoramidite (phosphate amide) (i.e. the R3, R4, R5 and R6 groups of compound (f) in Figure 5 (the instant elected species; Reply, filed 3/6/07)), as recited in **clms 18, 19, and 20**.

The reference also teaches various nucleobases such as C, A, and G (e.g. p. 204, Scheme 5), which read on the nucleotide bases recited in **clm 22** and the elected species of adenine.

Agris, teaches methods of monitoring the degree of deprotection “after” synthesis of oligonucleotides on arrays by detecting detectable protecting groups “remaining on the array” (e.g. Abstract; claims 14 and 50; p.9, [0158]+). The reference also teaches the need for such detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides can be carried out (e.g. p.1, [0005]).

Hobbs et al teach using various fluorescent molecules to label (or protect) nucleotides (see Abstract). The reference teaches “stilbene” can be used to attach to the nucleobases (col. 30, lines 20+) through linkers that comprise “carbonyl” group (reads on the formula of “COR” of **clm 21**; col. 11, lines 50+). The reference also teaches various fluorescent dyes can be used depending on the different applications (cols. 12+).

In addition, **Chen et al**, teaches attaching “stilbene” to nucleosides (see Abstract). The Chen reference also teaches “stilbene” has “bright fluorescence of very high quantum yield” (p. 1725, right col., para 2).

Art Unit: 1639

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to attach a fluorescent group such as “stilbene” to a “monomeric building block” (such as a nucleoside) to the amino groups of the nucleobase for various assays such as detecting the attached fluorescent group on an oligonucleotide array.

A person of ordinary skill in the art would have been motivated at the time of the invention to couple the protection group to the amino group of the nucleobase, because the nucleobase protection groups offer the advantages of providing more efficient and fast working oligodeoxyribonucleotide synthesis, as taught by Wagner et al (e.g. p.200). In addition, because both the McGall reference and the Wagner reference teach methods of using protected monomers (nucleotide building blocks) to generate oligonucleotides with detection of the degree of deprotection (for either the sugar phosphate groups or the nucleobase groups) that are necessary for completion of oligonucleotide synthesis, it would have been obvious to one skilled in the art to substitute one detection method of detecting the deprotection of the sugar phosphate reactive groups for the other (the deprotection of the nucleobase groups) to achieve the predictable result of determining the degree of deprotection for a solid state oligonucleotide synthesis.

A person of ordinary skill in the art would also have been motivated at the time of the invention to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides, because Agris teaches the need for such as a simple and reliable technique to control the quality of the synthesized microarray, as discussed *supra*. In addition, it would have been *prima facie* obvious for a person of ordinary skill in the art to use fluorescent groups (such as stilbene) as the protecting group and to measure the remaining

Art Unit: 1639

fluorescent signals after cleavage to assess the degree of protection, to improve the quality control assay for the deprotection step during an array generation (of methods such as McGall et al) for the predictable result of enabling routine oligonucleotide synthesis on an array with various known protection and labeling groups.

A person of ordinary skill in the art would have been motivated at the time of the invention to use “stilbene” as the “detectable protecting group”, because “stilbene” is a known fluorescent label for biomolecules (especially nucleotides), and stilbene is known to exhibit “bright blue fluorescence of very high quantum yield”, as taught by both Hobbs et al and Chen et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to use the specific nucleotide building blocks and their corresponding chemistry to generate the required reagent for the method of detecting deprotection, because the structures for basic nucleotide building blocks are known in the art, and the various protection groups are known and routine in the art as taught by Wagner et al. In addition, Wagner et al also teach the advantages of using these nucleotide building blocks and their corresponding protection groups, including providing efficient and fast working oligonucleotide synthesis as well as fast and effective cleavage of the protection group (e.g. pp.200-201).

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since McGall et al, Wagner et al, Hobbs et al and Chen et al have demonstrated successful attachment of various protection groups such as fluorescent groups (especially stilbene) to nucleosides through known reaction mechanisms (such as the formation

Art Unit: 1639

of -HN-C=O linkage between the nucleobases and the stilbene molecule) as well as using various nucleotide building blocks to build oligonucleotides, as demonstrated by the said references.

Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants' arguments are addressed with the following discussion as well as the above modified rejection (in light of applicant's amendment to the claims).

In general, applicants traversed the above rejection over a combination of references by attacking each reference alone. (Reply, pp.9+).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue the McGall reference does not teach or suggest "methods whereby quality of deprotection, in particular of protected amino groups, is determined". Applicants also assert the McGall reference is focused on "efficiency of synthesis" and failed to "address the problem of deprotecting reactive groups not involved in synthesis..." (Reply, p.9, para 4).

However, the above rejection is not over the McGall reference alone. Applicants are respectfully directed to the above rejection for detailed discussion how the combination of the reference teaches all elements of the instant claims. The alleged deficiency of the McGall reference is remedied by the above cited additional references (especially the Wagner reference). Briefly, the McGall reference explicitly teaches measuring “deprotection efficiency” of the various reactive groups on the building blocks in general (e.g. col.8, lines 53+). The McGall reference (see entire document; especially, cols 2 and 8-9) teaches, in general, using protected nucleotide building blocks (so that the various reactive groups on the nucleotides are protected from chemical reactions during synthesis) are necessary in synthesizing oligonucleotides (or biopolymers), and it is also necessary to “deprotect” these reactive groups for subsequent applications. The McGall reference mainly teaches protection/deprotection of the reactive groups on the sugar phosphate groups of the nucleotide building blocks, as discussed supra. Similarly, the Wagner reference teaches synthesis of various oligonucleotides using protected nucleotides (pp. 204-206; especially Table 1 and p. 204, last para). The Wagner reference specifically teaches using fluorescent protective groups that are linked directly to the amino group of the nucleobases (e.g. p. 202, Schemes 1-2), which protects the amino reactive group of the nucleobases. The Wagner reference also teaches measuring the efficiency of deprotection of the nucleobases at the completion of the oligonucleotide synthesis (e.g. e.g. pp.205-206; Figure on pg.206).

As discussed supra, because both the McGall reference and the Wagner reference teach methods of using protected monomers (nucleotide building blocks) to generate oligonucleotides with detection of the degree of deprotection (for either the sugar phosphate groups or the

Art Unit: 1639

nucleobase groups) that are necessary for completion of oligonucleotide synthesis, it would have been obvious to one skilled in the art to substitute one detection method of detecting the deprotection of the sugar phosphate reactive groups for the other (the deprotection of the nucleobase groups) to achieve the predictable result of determining the degree of deprotection for a solid state oligonucleotide synthesis.

Applicants also seem to argue there is no reasonable expectation of success. (Reply, p.9, last para).

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since McGall et al, Wagner et al, Hobbs et al and Chen et al have demonstrated successful attachment of various protection groups such as fluorescent groups (especially stilbene) to nucleosides through known reaction mechanisms (such as the formation of -HN-C=O linkage between the nucleobases and the stilbene molecule) as well as using various protected nucleotide building blocks to build oligonucleotides with subsequent deprotection reactions, as demonstrated by the said references.

Applicants also assert the references (especially McGall or Wagner reference) do not teach "complete deprotection of the protected reactive side groups". (Reply, p.9, last para; p.10, para 1+)

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "complete deprotection of the protected reactive side groups"; "complete deprotection of all protecting

Art Unit: 1639

groups...”) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The instant claim 1 recites in the preamble or method steps, “A quality control method for determining degree of deprotection...” or “a degree of deprotection”, which does not require “complete” deprotection as asserted by applicants. The instant claim 1 as written only requires assessing the “degree” (or the amount) of deprotection after the “cleavage” step (i.e. step (b)). The instant claims (e.g. claim 1) does not dictate that “all” reactive groups be deprotected “completely”. In addition, the instant claims (at least claim 1) recites “detecting detectable protecting groups remaining on the array”, which seems to require the cleavage of the protecting group to be “incomplete” (as some protecting groups “remain” attached). Thus, applicant’s assertion seems to be in contradiction to the explicit recitation of the instant claims.

Applicants are respectfully directed to the above rejection for detailed discussion of how the combination of cited references teaches all elements and renders the instant claimed invention obvious.

Applicants also argue the references (especially McGall or Wagner) fail to teach “on-chip” analysis (Reply, p.10, para 1-2).

However, the McGall or the Agris reference teaches on-array determination of protection and deprotection as discussed above. The combination of the cited references renders the instant claimed invention obvious. Briefly, the McGall reference teaches “determining the amount of unprotected active sites” (col. 2, lines 49+) by detecting the amount “detectable labels” on the

Art Unit: 1639

array (col. 2, lines 40+; cols. 8-9; Figure 7; especially, col.9, lines 9+), which teaches detection on the array. In addition, Agris, teaches methods of monitoring the degree of deprotection “after” synthesis of oligonucleotides on arrays by detecting detectable protecting groups “remaining on the array” (e.g. Abstract; claims 14 and 50; p.9, [0158] +). The reference also teaches the need for such detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides can be carried out (e.g. p.1, [0005]). Thus, a person of ordinary skill in the art would also have been motivated at the time of the invention to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides.

Applicants also assert the references do not teach the element of “deprotection at the termination of synthesis” (Reply, p.10, last para; p.11, para 2).

As discussed supra, the McGall reference teaches “deprotecting” (or removal) of the protecting group at the end of each round of synthesis (e.g. Claim 23; col. 2, lines 40+; Figure 9), which reads on step (b) of **clm 1**. The instant claim language (step b) of claim 1) can be broadly interpreted to mean after the termination of any synthesis step, for example, after each round of synthesis (i.e. after the end of each cycle). Because the instant specification does not specifically define the term “biopolymer” to be of any specific structure (or chain length), any biopolymers of any size/length can be viewed as a “synthesized biopolymer” given the reasonable and broad interpretation of the terms “synthesis” and “biopolymers”. The McGall reference teaches, for example, “photolabile groups” (i.e. protection groups) and “side chain protective groups” are removed after the desired products are produced (e.g. col.5, lines 2), which reads on the step of cleaving the protecting groups “after synthesis is terminated”. In addition, the Wagner reference

Art Unit: 1639

also teaches deprotecting the label attached nucleobase after the synthesis of the oligonucleotide (e.g. pp.205-206; Figure on pg.206), which also reads on the step of deprotection “after synthesis is terminated”. As discussed above, it is prima facie obvious to protect the nucleobase during oligonucleotide synthesis, and the step of deprotection (of the protected nucleobase) after synthesis is also necessary to form functional oligonucleotides (as taught by Wagner; entire doc.; especially, pp.200-201). Thus, it would have been prima facie obvious to deprotect the nucleobase reactive groups (i.e. removing the protecting groups) after synthesis termination of the oligonucleotides to provide functional oligonucleotide with normal nucleobase residues for any subsequent applications.

Applicants also briefly traversed the Hobbs, Chen and Agris references by asserting each of the said references does not teach all elements of the instant claims. (Reply, p.11, para 4).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

Art Unit: 1639

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Patent Examiner, Art Unit 1639
12/2/08